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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/GB88/00193 (22) International Filing Date: 11 March 1988 (11.03.88) (31) Priority Application Number: 8705985 (32) Priority Date: 13 March 1987 (13.03.87) (33) Priority Country: GB (71) Applicants (for all designated States except US): ED GEISTLICH SÖHNE A.G. FÜR CHEMISCHE INDUSTRIE [CH/CH]; CH-6110 Wolhusen (CH). HOLMES, Michael, John [GB/GB]; 15 Campion Road, London SW15 (GB). (72) Inventor; and (75) Inventor/Applicant (for US only) : WOKALEK, Heinrich [DE/DE]; Klinikum der Albert-Ludwigs Universität Freiburg , Hauptstrasse 7, D-7800 Freiburg (DE). (74) Agents: BOYES, Kenneth, Aubrey et al.; Frank B. Dehn & Co., Imperial House, 15-19 Kingsway, London WC2B 6UZ (GB).		(81) Designated States: DE, GB, JP, US. Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: DRESSINGS (57) Abstract A hydrogel sheet with capillaries permitting wound exudate to pass through the sheet while not permitting bacteria to infect the wound. The sheets do not stick to the wound surface and allow large quantities of wound exudate to be removed from the wound.		

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"Dressings"

The present invention relates to hydrogel dressings, their use and their manufacture.

Traditional wound dressings usually comprise a fabric or felt of absorptive material such as a gauze in direct contact with the wound. Such dressings are normally covered in order to avoid or reduce bacterial contamination but are not efficient in this respect. They have the general advantage of absorbing exudate from the wound but on the other hand, tend to stick to the wound surface, thus inhibiting healing. Furthermore, removal of the dressing is commonly painful where such sticking has taken place.

More recently, hydrogels have been proposed as wound dressings. The high water content of the gel is particularly compatible with the exposed surface of the wound and healing is significantly enhanced. There is in general no tendency to stick to the wound so that removal of the dressing is relatively painless.

A particular feature of such hydrogel dressings has been that they are impermeable to bacteria and thus serve to maintain the sterility of the healing surface, whereas fabric dressings, being porous, tend to permit bacterial invasion. This has been a significant factor in the promotion of hydrogel sheets for use as dressings.

In general, hydrogel dressings, even though moist, are able to absorb a moderate amount of exudate from the wound. However, where excessive production of wound exudate is encountered, the absorptive capacity of the hydrogel may be exceeded. It has been proposed to use hydrogel granules adhered to a non-porous backing in order to enhance absorption

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of exudate. In promotional literature on such products great emphasis has been laid on the impermeability of the backing and the resistance to bacterial invasion. However, there is some tendency for
5 the granular hydrogel to stick to the wound surface and require removal, thus hindering healing.

We have now found that the above problems may be combated particularly satisfactorily by using a dressing comprising a hydrogel in sheet
10 form with capillaries passing through the sheet. Excess exudate may then pass through the dressing and can be absorbed by a suitable absorptive dressing or compress placed over the hydrogel. If the size and numbers of such capillaries are suitably chosen,
15 it is possible to deal with excess exudate while avoiding the problem of bacterial invasion found with traditional porous dressings.

The invention thus provides hydrogel sheets for use as wound dressings, said sheets being provided
20 with capillaries which permit wound exudate to pass through the sheets while not permitting bacteria to infect the wound.

The capillaries are preferably of such diameter that the forces drawing liquid through the dressing
25 from the wound are adequate. If the capillaries are too narrow, proteins, cells and other solids will block the flow of liquid, although it has been observed that the capillary forces are unusually high due to the particular surface properties of
30 the hydrogel. If the capillaries are too wide, the capillary forces will be insufficient to draw liquid from the wound and may permit bacterial invasion.

Furthermore, the initial requirement of the
35 dressing is to permit or enhance removal of suppurating liquid from the wound. While this process continues and there is a positive flow of liquid away from the wound, bacteria will not be able to invade

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in a contrary direction. However, as the flow of liquid subsides, chains of protein material and cells will build up in the capillaries so blocking them and preventing bacterial invasion. Eventually, 5 a sheet of new tissue will develop which will completely block bacterial invasion. It will be appreciated that the relatively small area represented by the capillaries will not have any significant effect on the ease of removal of the dressing.

10 In general, the total cross-sectional area of the capillaries should represent 0.5 to 3.0% of the area of the hydrogel sheet, preferably 1 to 2%, e.g. about 1.5%. The capillaries may, for example be spaced 5 to 20mm apart, conveniently 15 in longitudinal and transverse rows; they will normally be of circular cross-section, having diameters in the range 0.5 to 3mm, preferably 1-2.5mm, e.g. about 2mm.

The hydrogel sheets will generally be between 20 2 and 10mm in thickness, preferably between 3 and 5mm, e.g. about 3.5mm. The lateral dimensions of the sheets may be adapted to the wound to be treated, e.g. by cutting.

The hydrogel sheets are preferably in accordance 25 with the disclosure of GB-A-1594389 and may thus comprise a gelable polysaccharide and/or protein or polypeptide interspersed with a polymer of a hydrophilic acrylic acid or methacrylic acid derivative. However, instead of the acrylic or methacrylic 30 acid derivative, other hydrophilic polymers may be used, for example polyvinylpyrrolidone. The hydrophilic acrylic or methacrylic acid derivative is preferably an amide, more preferably acrylamide, or an ester with an alkanol, optimally a polyol, 35 especially preferably a C₁₋₆ alkanol such as methanol or ethanol. Conventional bi- or polyfunctional cross-linking agents such as N,N'-methylene-bis-acrylamide may be used to cross-link the polymer.

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The gelable polysaccharide is preferably agarose or agar-agar while amongst gelable proteins and polypeptides, gelatine is preferred.

The water content of such a hydrogel can
5 be very high, for example in the range 95 to 98% by weight, preferably about 97%. Thus, the solid matrix of the gel may constitute only 2 to 5% by weight of the gel, preferably about 3%.

In general, the most preferred hydrogels
10 comprise (a) agar-agar together with (b) polyacrylamide cross-linked with about 2% by weight of N,N'-methylene bis-acrylamide, advantageously in the ratio range 1:3 to 1:4, preferably about 1:3.5. This gel, when fully swollen with water, contains about 96.5%
15 by weight of water. A gel of this type is now commercially available from Geistlich Pharma of Wolhusen, Switzerland under the Registered Trade Mark Geliperm.

Hydrogel dressings according to the invention
20 may be used in surgery in the preparation of the wound base for free skin transplantation; in the treatment of the donor site after the removal of split skin grafts in plastic surgery and for covering superficial operation wounds to prevent exposed
25 bradytrophic tissue (tendons, periostium, bone or cartilage) from drying out. In dermatology, the hydrogel dressings may be used in the treatment of both fresh and chronic damage to the epithelium e.g. after dermal abrasion; to encourage granulation
30 and the formation of cellular tissue in chronic ulcers, especially crural ulcers, decubitus sores etc; in the treatment of patients with polyvalent allergies when other forms of dressings and external applications are contra-indicated; and in the treatment
35 of superficial thrombo-phlebitis in combination with external therapeutic measures used in such cases.

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In general surgical debridement should be carried out to remove necrotic tissue prior to the application of the hydrogel sheet. Deep fissured wounds containing pockets of infected pus or necrotic tissue should be treated by appropriate therapeutic measures prior to the application of the sheet. Primarily strongly infected wounds should be treated with antimicrobial agents either prior to, or in combination with the hydrogel dressings

- 10 The hydrogel dressings should be changed in accordance with individual clinical preference. Where the dressings are left in situ for more than 24 hours under a dry dressing, regular irrigation with appropriate aqueous solutions (e.g. saline)
- 15 should be carried out to prevent dehydration. In instances where the hydrogel sheet has been allowed to dehydrate, rehydration should be carried out before removal.

- 20 A gauze dressing may be used to cover the hydrogel sheet and a compression bandage on top of it. This helps the patient keep mobile for instance in crural ulcer.

- It should be noted that the hydrogel sheets according to the invention are generally permeable
- 25 to salts, nutrients and antibiotics as well as proteins of higher molecular weight. However, since the hydrogel sheets are generally very pliable they can adapt themselves closely to the shape of the wound and promote coagulation, as is evident
- 30 particularly in cases of dermal abrasion. A further favourable factor is the plane compression of the wound base which prevents the formation of wound oedema and results in an improvement in the circulation of the blood in the wound area. A fibrin-wall,
- 35 rich in leucocytes forms between the hydrogel sheet and the surface of the wound, which may be interpreted as the body's own defensive barrier. Owing to this leucocyte-rich wall of fibrin which forms

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after the application of the hydrogel sheet, use of local antibiotics and other external applications is, in the case of chronic ulcers, as a rule superfluous, as these substances may, in fact, be found to inhibit
5 epithelial proliferation.

The hydrogel sheets according to the invention may be prepared from unperforated sheet of the hydrogel material, which may be substantially as described in GB-A-1594389. Thus, the capillaries
10 in the sheets may be provided by subsequent perforation.

However, on account of the very great pliancy of the hydrogel material, it is not normally sufficient simply to push a series of needles or thin rods through the sheets, since on removal of these,
15 the holes tend to close without leaving significant capillaries in the material. It is generally necessary, therefore, to remove cores of hydrogel material from the sheets to provide the necessary capillaries, e.g. using hollow needles or syringes, which are
20 conveniently connected to a vacuum line to assist removal of the material. The syringes will generally be slightly larger than the required capillaries, for example 0,5 to 5mm, e.g. 2.5 mm.

Alternatively, it is possible to form the
25 sheets in moulds provided with a series of upward projections such that on removal of the sheets from the mould, appropriate capillaries are formed.

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The following example is given by way of illustration only:

Example

- 5 20 g of agar-agar are suspended under agitation in 880 g of deionized water and heated to 95°C until complete dissolution. 1 litre of a second aqueous solution containing 70 g of acrylamide and 1.84 g of N,N'-methylene-bis-acrylamide is
10 prepared at ambient temperature and added to the first solution with thorough mixing. Under continued agitation, 2.2 g of N,N,N',N'-tetrakis-(2-hydroxypropyl)-ethylene diamine dissolved in 60 g of water and then 1.26 g of ammonium peroxodisulfate dissolved
15 in 40 g of water are added.

The mixture is poured into flat moulds (26 x 12mm) to a depth of 3mm.

- The mixture has a temperature between 50°C and 55°C and begins to polymerize immediately.
20 After 10 minutes the gel point is reached. The batch is allowed to cool down overnight during which time polymerization is completed.

- The gel is freed from soluble impurities by washing with pure flowing water for 24 hours.
25 With this washing the gel swells to 135% of its original weight. Such sheet material is now commercially available under the name Geliperm from Geistlich Pharma of Wolhusen, Switzerland.

- The sheets are then perforated with an array
30 of 2.5 mm syringes connected to a vacuum line, to provide rows of 2mm capillaries spaced at 15 mm intervals in both the longitudinal and lateral directions.

- The perforated sheets are placed in plastic
35 trays which are then heat sealed with clear plastic sheet. The sealed trays are then sterilised.

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CLAIMS:

1. A hydrogel sheet for use as a wound dressing, said sheet being provided with capillaries which permit wound exudate to pass through the sheet while not permitting bacteria to infect the wound.
2. A hydrogel sheet as claimed in claim 1 wherein
5 the total cross-sectional area of the capillaries represents 0.5 to 3.0% of the area of the said sheet.
3. A hydrogel sheet as claimed in claim 1 wherein
10 the capillaries are of circular cross-section with a diameter of 0.5 to 3 mm.
4. A hydrogel sheet as claimed in claim 1 having a thickness of 2 to 10 mm.
5. A hydrogel sheet as claimed in claim 1 comprising a gel selected from gelable polysaccharides, proteins
15 and polypeptides.
6. A hydrogel sheet as claimed in claim 5 comprising a gel selected from agarose, agar-agar and gelatine.
7. A hydrogel sheet as claimed in claim 6 wherein the gel comprises
20 (a) agar-agar and
(b) polyacrylamide cross-linked with about 2% by weight of N,N'-methylene-bis-acrylamide,
the ratio of (a) to (b) being in the range 1:3
25 to 1:4.
8. A hydrogel sheet as claimed in claim 1 having a water content in the range 95 to 98% by weight.

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9. A method of treatment of a wound in the human or animal body comprising the application to said wound of a hydrogel sheet according to claim 1, whereby wound exudate is drawn from the wound through the dressing by forces within the capillaries of the said hydrogel sheet.
10. A method as claimed in claim 9 further comprising the step of irrigating the dressing with an aqueous solution.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 88/00193

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) * According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁴ : A 61 L 25/00; A 61 L 15/01; A 61 F 13/00																																			
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Minimum Documentation Searched *</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 30%; text-align: left; border-bottom: 1px solid black;">Classification System</th> <th style="text-align: right; border-bottom: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="border-right: 1px solid black; padding: 5px; vertical-align: top;">IPC⁴</td> <td style="padding: 5px; vertical-align: top;">A 61 L 25/00; A 61 L 15/01</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *</div>			Classification System	Classification Symbols	IPC ⁴	A 61 L 25/00; A 61 L 15/01																													
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III. DOCUMENTS CONSIDERED TO BE RELEVANT * <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; text-align: center;">Category *</th> <th style="width: 70%; text-align: center;">Citation of Document, ** with Indication, where appropriate, of the relevant passages **</th> <th style="width: 20%; text-align: center;">Relevant to Claim No. **</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">X</td> <td>GB, A, 2131701 (JOHNSON & JOHNSON) 27 June 1984, see example 9; claims 1,4,12,27,36</td> <td style="text-align: center;">1,3</td> </tr> <tr> <td style="text-align: center;">Y</td> <td style="text-align: center;">--</td> <td style="text-align: center;">4-8</td> </tr> <tr> <td style="text-align: center;">Y</td> <td>FR, A, 2441390 (MAX PLANCK) 13 June 1980, see page 5, lines 14-25</td> <td style="text-align: center;">5</td> </tr> <tr> <td style="text-align: center;">Y</td> <td style="text-align: center;">--</td> <td style="text-align: center;">4-8</td> </tr> <tr> <td style="text-align: center;">Y</td> <td>FR, A, 2392677 (MAX PLANCK) 29 December 1978, see page 3, lines 19-23; page 5, lines 29-37; example 2; claims 1-8</td> <td style="text-align: center;">4-8</td> </tr> <tr> <td style="text-align: center;">A</td> <td style="text-align: center;">--</td> <td style="text-align: center;">4-8</td> </tr> <tr> <td style="text-align: center;">A</td> <td>US, A, 4587284 (H. LUISSI) 6 May 1986, see example 1; column 3, lines 63,64</td> <td style="text-align: center;">4-8</td> </tr> <tr> <td style="text-align: center;">A</td> <td style="text-align: center;">--</td> <td style="text-align: center;">1</td> </tr> <tr> <td style="text-align: center;">A</td> <td>EP, A, 0206830 (JOHNSON & JOHNSON) 30 December 1986, see claim 1</td> <td style="text-align: center;">1</td> </tr> <tr> <td colspan="3" style="text-align: center; padding-top: 10px;">-----</td> </tr> </tbody> </table>			Category *	Citation of Document, ** with Indication, where appropriate, of the relevant passages **	Relevant to Claim No. **	X	GB, A, 2131701 (JOHNSON & JOHNSON) 27 June 1984, see example 9; claims 1,4,12,27,36	1,3	Y	--	4-8	Y	FR, A, 2441390 (MAX PLANCK) 13 June 1980, see page 5, lines 14-25	5	Y	--	4-8	Y	FR, A, 2392677 (MAX PLANCK) 29 December 1978, see page 3, lines 19-23; page 5, lines 29-37; example 2; claims 1-8	4-8	A	--	4-8	A	US, A, 4587284 (H. LUISSI) 6 May 1986, see example 1; column 3, lines 63,64	4-8	A	--	1	A	EP, A, 0206830 (JOHNSON & JOHNSON) 30 December 1986, see claim 1	1	-----		
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<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents: **</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>																																			
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;"> Date of the Actual Completion of the International Search 8th June 1988 </td> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;"> Date of Mailing of this International Search Report <div style="text-align: center; font-size: 1.2em;">08 JUL 1988</div> </td> </tr> <tr> <td style="border-bottom: 1px solid black; padding: 5px;"> International Searching Authority <div style="text-align: center;">EUROPEAN PATENT OFFICE</div> </td> <td style="border-bottom: 1px solid black; padding: 5px;"> Signature of Authorizing Officer <div style="text-align: center;"> P.C.G. VAN DER PUTTEN </div> </td> </tr> </table>			Date of the Actual Completion of the International Search 8th June 1988	Date of Mailing of this International Search Report <div style="text-align: center; font-size: 1.2em;">08 JUL 1988</div>	International Searching Authority <div style="text-align: center;">EUROPEAN PATENT OFFICE</div>	Signature of Authorizing Officer <div style="text-align: center;"> P.C.G. VAN DER PUTTEN </div>																													
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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 9-10 because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv)

Methods for treatment of the human or animal body, by means of surgery or therapy as well as diagnostic methods.

2. ☐ Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers _____, because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 8800193
SA 21152

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 27/06/88. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP-A, B 0114481	01-08-84
		JP-A- 59120159	11-07-84
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		SE-B- 443514	03-03-86
US-A- 4587284	06-05-86	None	
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		US-A- 4655758	07-04-87